IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NATERA, INC.,	)	
	)	
Plaintiff,	)	C.A. No. 20-125 (LPS)
	)	(CONSOLIDATED)
v.	)	
	)	**JURY TRIAL DEMANDED**
ARCHERDX, INC., ARCHERDX, LLC and INVITAE CORP.	)	**FILED UNDER SEAL**
	)	
Defendants.	)	
	)	

DEFENDANTS' REPLY IN SUPPORT OF MOTION FOR SUMMARY JUDGMENT

Dated: February 25, 2022

Brian E. Farnan (Bar No. 4089)
Michael J. Farnan (Bar No. 5165)
FARNAN LLP
919 N. Market St., 12th Floor
Wilmington, DE 19801
(302) 777-0300
(302) 777-0301 (Fax)
bfarnan@farnanlaw.com
mfarnan@farnanlaw.com

Edward R. Reines (admitted *pro hac vice*)
Derek C. Walter (admitted *pro hac vice*)
Concord Cheung (admitted *pro hac vice*)
WEIL, GOTSHAL & MANGES LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065
Tel: (650) 802-3000
Fax: (650) 802-3100
edward.reines@weil.com
derek.walter@weil.com
concord.cheung@weil.com

Justin L. Constant (admitted *pro hac vice*)
WEIL, GOTSHAL & MANGES LLP
700 Louisiana, Suite 1700
Houston, TX 77002
Tel: (713) 546-5011
Fax: (713) 224-9511

Attorneys for Defendants

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I. REPLY ARGUMENTS IN SUPPORT OF SUMMARY JUDGMENT

A. Defendants Do Not Infringe the '482, '172, and '814 Patents

Natera does not deny that the "universal primer" element of the '482, '172, and '814 patents requires the universal primer in the second PCR to be the same as the universal primer in the first PCR. D.I. 442 at 1. Natera also does not dispute that the P5_1 and P5_2 primers used in the accused products have ***different nucleotide sequences***. *Id.* Natera's own expert, Dr. Quackenbush, testified that these primers "don't have the same base sequence." Ex. 1 at 188:24.

Natera nonetheless seeks to avoid summary judgment by pointing to Dr. Quackenbush, who stated that the P5_1 and P5_2 primers have 26 nucleotides in common. D.I. 442 at 2. But he never actually opines that the primers are identical—only that they have some overlapping nucleotides. At deposition, he was clear that the "primers don't have the same base sequence." Ex. 1 at 188:24-25. When asked to confirm that he believed the P5_1 and P5_2 primers were the same, Dr. Quackenbush testified that the question mischaracterized his testimony:

> Q Okay. So for the purposes of the claims in the '814, '482, and '172 patents, your opinion is that the P51 and P52 primers are the same; is that correct?
>
> MS. BENASSI: Objection. Mischaracterizes the witness's testimony.
>
> Q Did I mischaracterize your testimony?
>
> A Yes, I believe you did.

Id. at 189:5-13. Dr. Quackenbush thus cannot defeat summary judgment because he does not even purport to express the opinion Natera needs. Even if Dr. Quackenbush did opine that the first and second primers were the same, this would not matter because a "party does not manufacture more than a merely colorable dispute simply by submitting an expert declaration asserting that something is black when the moving party's expert says it is white…." *See Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1080 (Fed. Cir. 2005).

Natera further contends that the Defendants admitted in FDA submissions that the primers

are the same. D.I 442 at 1-2. Defendants' FDA submissions, while accurate, were never intended to show every last detail of Defendants' products, including whether the primers used are exactly the same. Whatever Defendants include in an FDA submission does not change the undisputed fact that the first and second primers in the accused products are, in fact, different.

As to DOE, Natera says nothing to rebut application of the disclosure-dedication rule. Natera contends that the patents do not disclose primers that differ by [redacted] bases as "an alternative to a second universal primer consisting only of the sequence of the first universal primer." D.I. 442 at 4. Yet, applicability of the rule does not turn on whether a patent discloses, but leaves unclaimed the precise accused embodiments. The rule only requires that one "understand the unclaimed disclosed teaching upon reading the written description." *PSC Comput. Prods., Inc. v. Foxconn Intl.*, 355 F.3d 1353, 1360 (Fed. Cir. 2004). Further, the rule is not "one of form requiring us to identify some language specifically stating that an embodiment is an 'alternative.'" *CSP Techs., Inc. v. Sud-Chemie AG*, 643 F. App'x 953, 958-59 (Fed. Cir. 2016).

Here, there is no dispute that the specifications expressly disclose non-identical primers in consecutive PCRs as an alternative to identical primers. The specification teaches that, "[i]n some embodiments, the primer pairs used in the first and second round of PCR are different." D.I. 433-1, Ex. 1 at 7:19-20; *see also* Ex. 2 at 119:16-122:2. Likewise, the specification teaches that, in other embodiments, "the primer pairs used in the first and second round of PCR are the same." D.I. 433-1 at 7:21-22. This express disclosure of alternatives could not be clearer. Further, any contention that the skilled artisan would not recognize that the P5_1 and P5_2 primers with [redacted] different base pairs as being within the scope of the disclosed, but unclaimed, embodiments with different primers is not credible. The patent states that "[d]ifferent primers refers to non-identical primers." *Id.* at 37:57. The most natural way for two primers to be "non-

identical" is for them to differ by a few bases.

Natera cites *Eli Lilly & Co. v. Hospira, Inc.*, 933 F.3d 1320, 1334 (Fed. Cir. 2019). If anything, that case serves as a factual counterpoint and illustrates precisely why the rule applies here. In *Eli Lilly*, skilled artisans would have been totally unable to discern that a particular chemical compound, pemetrexed ditromethamine, was disclosed, and hence dedicated to the public. The patent in that case at most disclosed "ammonium salts generally, which is far from a description of tromethamine." *Id.* at 1335. Given the thin disclosure, the Federal Circuit found no reason to believe that a skilled artisan would set out on a "winding path to cobble together pemetrexed ditromethamine." *Id.* at 1335. Here, by contrast, everyone agrees that the specification expressly teaches different universal primers, and that primers are "different" simply by virtue of being "non-identical," which is true of the P5_1 and P5_2 primers. The disclosure-dedication merely requires the "ability to discern both what has been disclosed and what has been claimed …." *PSC Comput. Prods., Inc.*, 355 F.3d at 1360. That is satisfied here.

Natera further argues that the '220 patent "rebuts an inference of dedication" because it claims non-identical universal primers. D.I. 442 at 3 n.2. As Defendants previously explained, however, both Federal Circuit law and cases from this Court are clear that the disclosure-dedication rule cannot be retroactively switched off by filing a continuation. *See, e.g.*, *CSP Techs., Inc.*, 643 F. App'x at 958; *In re Bendamustine Consol. Cases*, No. 13-cv-2046, 2015 WL 1951399, at *3 (D. Del. Apr. 29, 2015).[1] The patentee's choice to claim non-identical primers in the '220 patent and not in the other patents "implies an intent for the two [sets of] patents to cover different claim

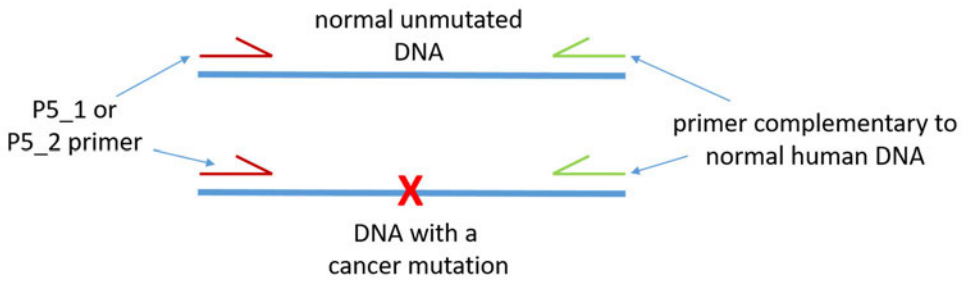
[1] Natera cites *Guardant Health, Inc. v. Foundation Medicine, Inc.*, Nos. 17-1616 & 17-1623, D.I. 437 at *24 (D. Del. May 7, 2020). *Guardant*, however, is an unpublished Report and Recommendation. To the extent it is understood as supporting Natera, it is contrary to Federal Circuit law and decisions from this Court and is wrong.

scope." *CSP Techs., Inc.*, 643 F. App'x at 958. The Court should grant Defendants' motion and reject Natera's attempt "to erase this distinction between its two [sets of] patents." *Id.*

B. Defendants' Cell-Free DNA Products Do Not Infringe

Natera does not deny that the Court's construction of "target loci" requires amplification of DNA from only a single individual. Nor does it deny that in the context of a cancer patient, the tumor is a "first individual" while a patient is the "second individual." Both Natera and its experts have said this. D.I. 430 at 12; Ex. 3 at 45:45-50. Natera's sole response to Defendants' motion is that the Court's construction does not exclude situations where the sample has a mixture of DNA from two individuals, as long as one amplifies the DNA of just one individual. D.I. 442 at 10. Natera points to cell-free DNA from a pregnant woman, which has DNA of both the fetus and mother, and notes that one could practice the claims by only targeting Y chromosome fragments, which can only be from one individual (*i.e.*, a male fetus). *Id.*

The problem for Natera is that this situation is inapplicable here. The accused products amplify ***both*** tumor and normal DNA. This is so because the primers used are (1) P5_1 or P5_2 primers (shown in red below) that are complementary to adaptor sequences and (2) primers that are complementary to normal human DNA (shown in green below). As shown below, these primers amplify ***both*** normal and tumor DNA, the latter of which is identical to normal DNA except for the cancer-causing mutation that is ***interior*** to the primers:



Natera nonetheless asserts—without a shred of evidence—that the "accused products target

tumor DNA." *Id.* Natera cites no evidence because it is simply incorrect that the accused products amplify only tumor DNA. This can be proven simply by looking at the primer sequences in the accused products. As set forth in the accompanying declaration of Concord Cheung, the primer sequences match 100% to the sequences of normal human DNA, such that they will necessarily amplify ***both*** normal DNA and tumor DNA, which is otherwise identical to human DNA except for mutations. *See* Chueng Decl. ¶¶ 9-11.

While the foregoing alone establishes that summary judgment is warranted, there is ample confirmatory evidence. Natera's expert, Dr. Quackenbush, has repeatedly confirmed that cell-free DNA of a cancer patient contains both tumor and normal DNA. *See* Ex. 4 ¶¶ 48-54; Ex. 5 ¶ 54. And, Defendants' internal documents show that their products determine an "allele fraction" reflecting the amount of mutated tumor DNA relative to normal DNA. *See, e.g.*, Ex. 6 at 43-55; Ex. 7 at 2; Ex. 8 at 35, 45, 135-36; Ex. 9 at 2634; Ex. 10 at 11 (Table 9). Such a "fraction" could never be computed if only tumor DNA were amplified. Summary judgment is thus warranted.

C. Defendants Do Not Infringe The '708 Patent

1. Natera Mischaracterizes The Construction Of "At Least 2 Primers"

Natera continues to argue that the claim element is met if only ***some*****,** but not all, of the primers in a PCR have a melting temperature less than the annealing temperature. D.I. 442 at 7. As the Court explained during claim construction, however, Natera distinguished the prior art from the claim language on the basis of the prior art not disclosing ***all*** of the primers having melting temperatures less than the annealing temperature. *See* D.I. 243 at 11; Ex. 11 at 14. Likewise, during prosecution, Natera specifically characterized the alleged invention as raising the annealing temperature above the melting temperature of all of the primers to mitigate primer dimer formation during multiplex PCR. Ex. 11 at 13. Based on the prosecution disclaimer, the Court held that the annealing temperature must be "greater than ***each*** of the melting temperatures of ***each*** primer,"

not an unspecified subset of 2 primers in the population. D.I. 243 at 11 (emphasis in original).

Natera's flawed interpretation—which the Court has rejected—contradicts the claim language. The claim language recites "***the*** at least 2 primers," and thus refers to the antecedent in the claim, which is "***a library of at least 2 primers*** that simultaneously hybridize to at least 2 of the target loci to produce a reaction mixture." Thus, "the at least 2 primers" must refer to "a library of at least 2 primers," and include ***all*** of the primers in the reaction. Because Natera does not deny that only some, but not all, of the primers in the accused products have melting temperatures below the annealing temperature, summary judgment is warranted.

2. Natera Mischaracterizes The Construction Of "Melting Temperature"

Natera does not deny that primers in the Accused Products include at least 2 segments: one that is complementary to the target sequence, which Natera calls a "complementary segment," and one that is not, which Natera calls a "tail segment." D.I. 442 at 7-8. Nor does Natera deny that the melting temperatures of all primers in Defendants' products are greater than the annealing temperature when the whole primers are considered. Natera, however, argues that the Court's construction for "melting temperature"—"the temperature at which one-half (50%) of a DNA duplex of each primer and its perfect complement dissociates and becomes single strand DNA"—refers only to the "complementary segment" of the primer.

The Court's construction of "melting temperature" was drawn directly from an explicit definition in the patent. D.I. 243 at 11. This definition is as follows:

> The melting temperature (Tm) is the temperature at which one-half (50%) of a DNA duplex of an oligonucleotide (***such as a primer***) and its perfect complement dissociates and becomes single strand DNA.

D.I. 17-2 at 79:28-31. This refers to the "perfect complement" of the "primer," not just part of the "primer." Had the patentee wished to state that melting temperatures of oligonucleotides, such as a "primers," should be computed on the basis of only parts of the primers, it would have

said so instead of referring to the whole "primer." Neither Natera nor its expert rebut the intrinsic evidence cited by Defendants confirming that when the patent refers to a "primer" it means the whole primer, including "tails" that are not complementary to the target. *See* D.I. 430 at 8-9.

Natera at most asserts, without citing any evidence, that the Court's construction only encompasses part of the primer because "the tail does not bind and does not form part of the duplex that the Courts [sic] construction requires." D.I. 442 at 8. This, however, is wrong. *See* D.I. 430 at 9-10 (citing D.I. 434, Ex. DD at 175:20-178:6.). As Defendant's expert made clear, "[o]nce you amplify, you produce amplicons that go from one tail to the next, and so I have PCR reactions that include the entire thing." D.I. 434, Ex. DD at 177:13-15. Natera never rebuts this. As such, summary judgment is warranted.

3. Natera Failed To Meet Its Burden To Prove Infringement

Natera does not deny that it relies solely on Defendants' documents as evidence of infringement. Natera, however, also does not deny that it has no idea how the melting temperatures in those documents were determined.

Natera nonetheless argues that summary judgment is unwarranted because Defendants could have shown that the values in their documents were not determined using a method disclosed in the patent. *See* D.I. 442 at 9. Yet, it is Natera's burden to prove infringement, not Defendants' burden to disprove it. In a footnote, Natera asserts in passing that Defendants "withheld" information needed to compute appropriate melting temperatures. D.I. 442 at n.6. Yet, Natera did not actually direct a single interrogatory or deposition question to the topic of how the melting temperatures in Defendants' documents were computed, and it tellingly cites no discovery requests that sought such information. Natera just failed to meet its burden here.

Natera cites the deposition of ArcherDx scientist Dr. Ryan Walters as supposedly showing that Primer3 was likely used to calculate the values in Defendants' documents. *See* D.I. 442 at

9. Natera, however, never questioned Dr. Walters about the documents relied upon by its experts, which Defendants specifically identified in discovery as disclosing the primer sequences in their products. Ex. 12 at 10-11. Natera instead asked Dr. Walters only about a random document that happened to include melting temperatures. As to this utterly irrelevant document, Dr. Walters testified that [redacted] Ex. 13 at 135:21-136:7. Dr. Walters' testimony does not help Natera, and summary judgment is warranted.

D. The '708 Patent Is Invalid In View Of Blomquist

Natera argues that Blomquist does not invalidate the '708 patent because it does not disclose "reaction conditions" where the annealing temperature is greater than the primer melting temperature. Natera contends that the claimed "reaction conditions" refer to ***all*** conditions ***throughout*** an entire PCR experiment, and that in Blomquist the annealing temperature is only greater than the melting temperature for part of the PCR experiment. The open-ended claim language in the '708 patent leaves no room for Natera's argument.

The claim term "reaction conditions," as Natera agrees, refers to the antecedent "primer extension reaction conditions." *See* D.I. 442 at 11. Thus, the "reaction conditions" are not for the entirety of a PCR experiment, but merely for "primer extension," which is only ***part*** of PCR. As Natera's own expert explains, three steps—denaturation, annealing, and extension—form a PCR cycle that is repeated to amplify DNA. Ex. 14 ¶ 46. During extension, he explains, there is "'extension' from the primers to form double-stranded segments through the addition of complementary nucleotides by DNA polymerase." *Id.* ¶ 45. By their very name, the "primer extension reaction conditions" refer to the conditions for this step, not the entire PCR.

Because the '708 patent claims use the open-ended "comprising" form, they are satisfied so long as one cycle of a PCR protocol uses "primer extension reaction conditions" where the

annealing temperature is greater than the melting temperature. They remain satisfied even if there are additional, unclaimed steps in the PCR protocol that uses "primer extension reaction conditions" where the melting temperature relationship is not satisfied.[2] This follows from basic black-letter law on the open-ended "comprising" claim form, for which no citation is needed.

As shown below, in Blomquist, there are 20 PCR cycles where the primer extension conditions have an annealing temperature (72°C down to 69°C in 1°C steps every 5 cycles) is above the 68°C melting temperature:

> Each competitive multiplex reaction mixture was cycled in an air thermal cycler (RapidCycler; Idaho Technology, Inc. Idaho Falls, Idaho) for a total of 45 cycles under modified touchdown PCR conditions with low primer concentration: 95°C/3 min (Taq activation); 5 cycles of 94°C/30 sec (denaturation), 72°C/4 min (annealing), and ***72°C/15 sec (extension)***; repeat 5 cycles with annealing temperature decreased 1°C to 71°C; iterate 1°C decrease and 5 cycles until annealing temperature was 64°C.

Ex. 15 at 6; *see also* D.I. 419-10 ¶¶ 259-61. Thus, Blomquist satisfies the claims.

Natera cites *Guardant Health v. Foundation Medicine, Inc.*, No. CV 17-1616-LPS-CJB, 2020 WL 1329513, at *4 (D. Del. Mar. 23, 2020) for the proposition that "comprising" "does not remove" limitations. This principle is inapplicable here because Defendants' position is not based on removing limitations from claims. As shown above, Blomquist undisputedly discloses "primer extension reaction conditions" where the annealing temperature is greater than primer melting temperatures. It also discloses additional discrete steps where the annealing temperature is less than the melting temperature, but these are irrelevant given that the claims' use of the "comprising" form.

For dependent claims 9 and 19, Natera provides no rebuttal beyond its claim 1 argument,

[2] In this regard, it is noteworthy that the patent specifically describes multiple rounds of PCR, particularly with different conditions. *See, e.g.*, D.I. 17-2 at 70:51-52, 234:20-30.

which fails for the reasons stated above. Summary judgment is thus warranted.

E. The Claims Are Not Enabled

1. Defendants Do Not Blow The Specification "Out of Proportion"

Natera proclaims that "[n]othing in the Asserted Patents remotely suggest that the claimed methods would not 'work' unless the specific primer design technique invented by Natera is employed." D.I. 442 at 18. The patents, though, teach that the techniques to remove such primers are "essential:"

> At high multiplexing it is not possible to eliminate all spurious interactions, but it is ***essential*** to remove the primers or pairs of primers with the highest interaction scores in silico as they can dominate an entire reaction, greatly limiting amplification from intended targets.

D.I. 78-1, Ex. 5 at 54:46-50; *see also id*. at 3:4-9; D.I. 419-10 ¶ 770.

Natera's response is to complain that Defendants blow this disclosure "out of proportion" because it is allegedly only a "single statement." D.I. 442 at 19. No law stands for the proposition that such unequivocal disclosure can be disregarded if it is only a "single statement." Even if there were such law, it would be inapplicable here because there is overwhelming additional evidence in the intrinsic record about the importance of primer design techniques to the alleged invention. *See, e.g.*, D.I. 177 at 13-17.

Any suggestion that primer design techniques to select sequences are not "essential" is put to rest by the testimony of Natera's experts. As Defendants explained, Natera's invalidity expert, Dr. Spellman, testified that without such techniques the PCR "does not work" and "you will get garbage." *See* D.I. 430 at 27. Natera's other technical expert, Dr. Quackenbush., testified that one would understand from the specification that to perform the claimed invention, the primer design techniques in the specification would be used "to avoid the formation of primer dimers:"

> So again, one skilled in the art would understand that in doing this nested PCR, one would design those primers as instructed by the written description using a tool

> such as Primer3, which is what the patent teaches us to use, and to ***do that in a way to avoid the formation of primer dimers***.

D.I. 434, Ex. L at 150:4-13, 150:25-151:5.

Natera nonetheless claims that Defendants have "no testimony on point," asserting that its experts were only testifying about "primer design ***in general***." D.I. 442 at 20 (emphasis in original). According to Natera, its experts were merely stating that primers must meet mundane requirements, such as being complementary to the target and having the "right orientation." *Id.* This is incorrect. Dr. Spellman's testimony that the claimed large scale multiplex PCR "does not work" and would yield "garbage" was in response to questioning about what would happen "if you didn't go through the process of identifying the pairs of primers that are likely to cause primer dimers and eliminating those" and "what would happen if you didn't go ahead and remove those primers that were likely to cause primer dimers." D.I. 434, Ex. B at 206:6-16, 206:22-207:5. The additional cited testimony from Dr. Spellman was in response to questioning about "selection of primers for the purpose of attempting to avoid primer dimers." *Id.* at 194:21-195:5; *see also* 196:4-197:1, 198:6-199:4. And Dr. Quackenbush's testimony was about choosing primers "in a way to avoid the formation of primer dimers" "as instructed by the written description using a tool such as Primer3." D.I. 434, Ex. L at 150:4-13, 150:25-151:5.

The cited testimony from Natera's experts is thus not "taken out of context," "cherry picked," "selective," or "rhetorical sleight of hand." D.I. 442 at 20, 22-23. It was about the exact thing the Court construed the claims to not require: selection of primer sequences to avoid primer dimers. *See* D.I. 430 at 24-25. The alleged innovations in this area are what the patents describe as a "surprising discovery" and what Natera's expert even relies upon to establish non-obviousness.[3] D.I. 434, Ex. A ¶¶ 205-06. Yet, during claim construction, Natera asserted that

[3] Natera claims that its expert was only relying upon this for non-obviousness of the '708 patent.

it had invented a way of doing large scale multiplex PCR ***without*** such techniques. *See* D.I. 185 at 34:9-18; *see also id.* at 6:3-10, 6:19-7:2, 12:12-22. Although the Court gave Natera a construction to this effect, the evidence has since proven that its assertion was wrong. Now, Natera's patents are not enabled under *Liebel-Flarsheim.*

2. Natera Cites Nothing In The Specification To Show Enablement

Given Natera's characterization of the specification as a "rich trove of detailed information," it is surprising how little Natera cites from the specification to rebut the foregoing evidence. D.I. 442 at 29. What little Natera cites does not undo the disclosure in the specification about primer design being "essential," nor does it show that there are "multiple inventions" in the specification, as Natera contends. *Id.* at 19.

Natera first cites a passage at 83:36-84:3 of the '814 patent allegedly stating that "highly multiplexed targeted PCR" can be performed "in a highly efficient manner" "without" primer design by using "partial or full nesting." D.I. 442 at 18.[4] The patent does not say this. It merely states that nesting can be "highly efficient." This enables nothing, let alone the claimed PCR reactions that encompass an unlimited number of target loci. Any claim that such techniques are enabled simply by using "partial or full nesting" is empty because Natera agrees it did not invent nested PCR and that nesting had long been known in the prior art. *See, e.g.*, D.I. 441 at 34-36; *see also* D.I. 419-10 ¶¶ 154-63. Natera's expert says there had been a long-felt need for ways of doing large scale multiplex PCR without forming primer dimers. D.I. 434, Ex. A ¶¶ 202-03. If the only thing needed to do multiplex PCR with hundreds of thousands of targets

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D.I. 442 at 30 n.16. That is wrong. Dr. Spellman's testimony was about "multiplex PCR" and the "claimed inventions" generally. *See* D.I. 434, Ex. A ¶ 204-06.

[4] Natera also cites a duplicate version of this passage in the '708 patent at 82:53-83:7.

were nesting, then researchers would have been doing it years before Natera's alleged invention. Nothing in the patents say that the mere use of "partial or full nesting" enables this.

Natera next points to the '814 patent at 97:36-38, 98:4-8, 30-33, contending based on this that "experiments were conducted using the one-sided nested PCR, hemi-nested or triply hemi-nested workflows." D.I. 442 at 19. This is true; such experiments were carried out. But it is undisputed that every working example in the patent was actually carried out using primer design techniques. *See* D.I. 419-10 ¶¶ 834-36. Natera conspicuously avoids the examples that make this clear, instead citing passages that merely give background on prior art nested PCR and that ***omit*** any discussion of the primers that were actually used for the experiments, which is revealed elsewhere in the patent. Again, if the only thing needed to do large scale multiplex PCR was nesting, researchers would have been doing it years before Natera.

Natera finally cites some passages in the '220 patent at 54:58-61, 91:12-16, 98:32-32, 213:3-8, which allegedly state that nesting can help make PCR better. D.I. 442 at 19. Perhaps true, but it does not show that skilled artisans could perform the claimed inventions ***without*** primer design techniques. In fact, the passage at 54:58-61 is part of the teaching that it is "essential" to employ such techniques for high multiplexing. Likewise, the cited passage at column 213 is part of Example 7, which is a 1,200-plex PCR where primer design techniques were, in fact, employed to yield the result that 73% of sequenced fragments mapped to the target. This is clear from the specification, which contrasts this result from a situation where, without primer design (*i.e.* "design and selection of assays"), the result was, in Dr. Spellman's words, "garbage:"

> An experiment was performed using this protocol using 1200-plex amplification. Both genomic DNA and pregnancy plasma were used; about 70% of sequence reads mapped to targeted sequences. Details are given elsewhere in this document. ***Sequencing of a 1042-plex without design and selection of assays resulted in >99% of sequences being primer dimer products***.

D.I. 433-1, Ex. 4 at 96:22-28; *see also* D.I. 419-10 ¶ 835 at 319-20. Natera cites nothing in the

patent showing working embodiments without primer design techniques. Natera's patents do not enable such techniques, and they are invalid under *Liebel-Flarsheim.*

F. The Claims Lack Adequate Written Description Support

Natera contends that Defendants' expert, Dr. Cooper, "undercuts" the contention that the specifications fail to describe the claims as an integrated whole. D.I. 442 at 25. Natera presents a chart that purports to show Dr. Cooper agreeing that Figure 6 discloses all the elements of claim 1 of the '814 patent. Natera thus submits Figure 6 as its best candidate for a disclosure of the claimed invention as an integrated whole.

Figure 6, however, falls far short. The alleged point of novelty of Natera's claims is large scale ***multiplex*** PCR, *i.e.*, PCR of ***multiple*** targets at the same time in the same reaction volume without unwanted side products. Natera's claims ***exclude*** PCR on a single target, claiming only PCR on "***at least*** ten target loci" up to infinity targets. Yet, Natera's chart ignores the "at least 10 target loci" requirement. *Id.* at 25-26. Figure 6 shows only a single nucleic acid target. Figure 6 cannot establish possession of the invention because it does not even disclose the thing that is allegedly inventive. Natera also ignores claim elements reciting a "sequencing tag" in the second PCR round and also the use of "high throughput sequencing." *Id.* at 25-26.

As to the other asserted patents, Natera never even bothers to present a chart based on Figure 6. These patents include yet additional claim elements absent from Figure 6, such as adaptors with "molecular barcodes" ('172, '220, and '482 patents), different "universal primers" in the first and second PCRs ('220 patent), 80% of the amplicons mapping to the target ('482 patent), and an annealing temperature greater than the melting temperature ('708 patent).

It is no wonder that Figure 6 of the patent does not describe the claimed inventions as an integrated whole because it is nothing more than an overview of one-sided nested PCR on a single target, which everyone agrees is not the invention, but just a prior art technique. *See* D.I.433-1,

Ex. 4 at 98:9; *see also* D.I. 433-3, Ex. 12 ¶ 14 (explaining that the disclosure cited by Natera is "prior art one-sided semi-nested PCR."); D.I. 444-36 at 120:4-15. Natera's own expert confirmed that one-sided nested PCR is not Natera's invention, but rather a known prior art concept. *See* D.I. 444-28 at 128:6-9, 144:7-11.

Other than Figure 6, Natera points to nothing that supposedly describes the claimed invention as an integrated whole. Natera points to ¶¶ 43-49 of Dr. Spellman's report as supposedly showing that the "priority applications expressly describe the steps as arranged in the claims." Yet, all of this material pertains to the '508 application, an ***October 2011*** application that Natera has given up on as actually supporting the claims. Indeed, Natera asserts in its brief that the "cfDNA Patents are entitled to priority date of ***November 18, 2011***." D.I. 442 at 28. At deposition, Dr. Spellman was clear that the October 2011 application does not describe the claims. D.I. 434, Ex. B at 182:23-183:4. And, in fact, ¶¶ 43-49 of Dr. Spellman's report draws from several different portions of the October 2011 patent application, each separated by tens of pages to try and cobble together the claims from unrelated portions of the document. *See* D.I. 443-16 ¶¶ 43-49 (citing material at pp. 115, 121, and 134 of the '508 application).

Natera next points to ¶¶ 49-57 of Dr. Spellman's reports as allegedly showing that the priority applications teach "molecular barcodes" and "sequencing." Yet, almost all of what Dr. Spellman cites again comes from the '508 application, which Natera admits does not show possession of the claims. To the extent the cited passages describe "molecular barcodes" and "sequencing," they are unconnected to the multiplex nested PCR schemes that Natera cites elsewhere, including Figure 6, and merely describe the use of barcodes to count molecules in the context of non-invasive prenatal testing as a stand-alone concept.

Natera ultimately resorts to the argument that the skilled artisan "would understand how

molecular barcodes and sequencing tag are used in the claimed methods, which is further supported by Dr. Cooper's opinion that molecular barcodes and high throughput sequencing were well known in the art." D.I. 442 at 27-28. This is merely an attempt to substitute obviousness for true written description, which Natera cannot do because a "description that merely renders the invention obvious does not satisfy the requirement." *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010).

Throughout this case, Defendants have repeatedly asked Natera to identify anything in the patents that they believe lays out the claimed inventions in an integrated whole. During discovery, Defendants propounded an interrogatory to this effect, which Natera responded to by citing the entirety of its 200-column specification. *See* D.I. 434, Ex. T at 34-37. Natera attempts to justify this non-answer as being due to the specification being such a "rich trove of detailed information" that it could not avoid citing anything less. D.I. 442 at 29. Nonsense. If Natera's patents had a good disclosure that laid out the claim as an integrated whole, Natera would have said so rather than resort to evasion by scattershot.

Then, at deposition, Defendants asked Natera's invalidity expert, Dr. Spellman, to identify something in the patents that disclosed the claims as a discrete package. As the expert who opined on written description and priority for Natera, one would have expected him to have solid answers. But he identified nothing. *See* D.I. 430 at 33-35. Natera attempts to explain this away as "cherry-picking" of testimony, citing transcript that allegedly shows Dr. Spellman had decent answers. D.I. 442 at 29. The Court, however, should look at this testimony, because it is either conclusory, irrelevant, or simply shows Dr. Spellman again failing to identify disclosure supporting the claims. *See* D.I. 443-3 at 185:2-21, 186:21-23, 189:4-21, 263:7-264:1. It confirms that Defendants did not "cherry-pick" evidence, and does not create an issue of fact.

Now, at summary judgment, Natera again fails to identify anything that describes the claims as an integrated whole. Although Natera emphasizes Figure 6, this does not even disclose the point of novelty of the alleged invention. It is telling that at the end of this case and after fact and expert discovery, the very best that Natera can point to as written description for its alleged invention is something that does not even disclose the key novel feature of its alleged invention.

Beyond failing to disclose the claimed steps as an integrated whole, Natera's patents also fail to establish that the inventors were in possession of techniques for large scale multiplex PCR without primer design techniques to avoid primer dimers. Just the opposite, the patent describes these techniques as "essential," not optional. Such disclosure is decisive on written description because, if the inventors truly possessed methods for carrying out multiplex PCR without such primer design techniques, they would never have described them as "essential." Although Natera urges the Court to disregard this as a "single statement" that Defendants are blowing "out of proportion," the public is entitled to take the patentees at their word about what is "essential."

Natera does not deny that every working example in the patent discloses the use of primer design techniques, and, as documented above, its experts confirmed that the skilled artisan would understand from the patent that such techniques should be used and that without them the result would be "garbage." Because the Court has construed the claims to cover multiplex PCR techniques without such techniques, and because this is not described, the claims are invalid.

G. Summary Judgment Of Indefiniteness Of The '708 Patent Is Warranted

Natera's primary response to Defendants indefiniteness argument is to point out that, at the claim construction stage, the Court declined to find indefiniteness. Natera insists that the "record has not changed; no new relevant evidence is proffered." D.I. 442 at 14. But, as documented below, Natera never rebutted the original evidence, and, in any event, the record has in fact evolved so extensively that Natera has been forced to admit indefiniteness.

1. The Patent Does Not Point To Specific Melting Temperature Methods

Natera contends that the skilled artisan would understand from the patent that only the Primer3/SantaLucia and UV light methods should be used. Yet, rather than pointing to specific techniques, the patentees were clearly concerned only with preventing their patent from being narrowly construed as limited to certain methods, and they drafted their patent accordingly. They studiously qualified any disclosures of methodology to make clear that they were only for use "in some embodiments," as opposed to all embodiments. D.I. 430 at 16-17. Likewise, they repeatedly referred broadly to "the empirically measured or calculated Tm," which makes no mention of particular methods and could not by any more open-ended. *Id.* Having opted for breadth, Natera's claims are now unavoidably indefinite under *Dow v. Nova.*

Natera responds that the generic phrase "such as ***the*** empirically measured or calculated Tm" actually refers either the UV light or Primer3/SantaLucia methods because the phrase is not "such as ***any*** empirically measured or calculated Tm." D.I. 442 at 13-14.[5] Natera says "[n]o other method is expressly identified in the patent and Defendants point to none. Thus, a skilled artisan would understand the phrase 'such as the empirically measured or calculated Tm' in the specification to indicate generally the two methods identified in the patent." *Id*. at 14.

But if this were so clear, then why did Natera inform the public and Patent Office during prosecution that other techniques, such as the undisclosed Bolton and McCarthy method, can be used? *See* D.I. 430 at 18-20. Throughout this case, including since claim construction, Natera has never explained this. Natera alleges that its use of the Bolton and McCarthy method during prosecution is of no consequence because it allegedly "also used Primer3/Santa Lucia to calculate

[5] On its face, however, Natera's argument is flawed because "the" refers to the melting temperature and not the determination method. *See, e.g.*, D.I. 17-2 at 79:62-80:1.

melting temperature during that patent prosecution." D.I. 442 at 15-16. Even if true, however, this misses the point, which is that Natera ***admits*** skilled artisans would not understand its patents to point to particular methods for computing melting temperatures because Natera itself used something different than the methods it says its patents require.

What's more, Natera is wrong that it used the "Primer3/SantaLucia method" during prosecution. It could not possibly have done this because, as Natera admits, the "SantaLucia model is not valid for oligo longer than 35bp." D.I. 434, Ex. S at 4. In fact, Natera used an "in-house implementation of the SantaLucia model for primers greater than 37 bp." *Id.* at 2. Thus, during prosecution, Natera admitted not just that one could use the undisclosed Bolton and McCarthy methods, but also undisclosed "in house" variants.

Even as to the Primer3 software, Natera does not deny that the patent refers to both the Breslauer ("default") and SantaLucia ("recommended") options. Natera presents no reason why a skilled artisan would choose one over the other except to assert that there would be "no confusion" as of 2014. D.I. 442 at 15. This is without merit because the patent fails to provide any guidance as to which method was actually used. Experiment 25 discusses ***both*** methods, but fails to identify the primers or corresponding melting temperatures that would allow one to discern what method was used. Natera argues that the patent contains "over 200 pages of primer sequences." *Id*. at 15 n.11. This is irrelevant. None of these sequences even relate to Experiment 25. *Compare* D.I. 17-2 at 235:18-19 ("***3,168-plex*** reaction was performed with 3,168 primer pairs") *with id.* at 44:31-43 (referring to "1,200-plex," "2,686-plex," and "10,984-plex" libraries). Moreover, the patent does not provide melting temperatures for any primer in the "over 200 pages of primer sequences."

2. Natera Admits Indefiniteness

While Natera contends that the "record has not changed," it has in fact evolved dramatically

to the point where Natera has effectively admitted indefiniteness. This has happened because, while Natera originally argued that the Primer3/SantaLucia and UV light techniques yield results that are not materially different, it has been unable to sustain this position. As Defendants' expert established based on publicly available data, these two methods can yield results that differ by almost ten degrees. D.I. 430 at 21-22.

Unable to rebut this, Natera resorts to a new argument that ultimately proves indefiniteness. Specifically, Natera contends that one would not actually use the Primer3/SantaLucia method in the patent, but a method based on techniques developed by Owczarzy. As Natera states, the "Primer3/Santa Lucia software (***with the improvement made by Owczarzy and colleagues and available as of the 2014 priority date of the '708 Patent***) could determine melting temperature values within 1°C difference from that measured using the UV light method." D.I. 442 at 16. This is critical because, as Defendants previously explained, the Owczarzy techniques are totally absent from the patent, even though they were allegedly available before the priority date. *See* D.I. 441 at 3-4. While the patent refers to version 2.2.3 of Primer3, Owczarzy is not implemented in this software. To the extent later, but unmentioned, versions of Primer3 implemented Owczarzy, those version instruct that Owczarzy should not be used. *Id.* at 4-5.

Natera asserts that the skilled artisan would necessarily understand that either the Primer3/SantaLucia or UV light methods should be used because "[n]o other method is expressly identified in the patent and Defendants point to none." D.I. 442 at 14. Having emphasized the importance of express disclosure, it is peculiar that Natera now makes the ***undisclosed*** Owczarzy technique so central. Regardless, given Natera's reliance on Owczarzy as necessary to bring the two techniques mentioned in the patent into alignment, Natera admits that the patent at most teaches two ***different*** techniques that give ***different*** results. This proves indefiniteness.

3. Natera's Arguments Regarding Reaction Conditions Are Flawed

Natera asserts that the "reaction conditions are important for primer melting temperature calculations." *Id*. at 16-17. Defendants agree. It is precisely because the conditions are important and precisely because the patent fails to disclose a particular set of conditions that the claims are indefinite. *See* D.I. 430 at 23. Natera, however, argues that the claims themselves direct a skilled artisan to utilize the "reaction conditions" for determining primer melting temperature. On its face, however, the term "reaction conditions" in the claim qualifies "annealing temperature," not "melting temperature." Natera contends that the Court "rejected" this argument during claim construction. D.I. 442 at 16. In fact, the Court did not address this in its claim construction opinion. *See* D.I. 243 at 10-12. As Defendants established, the patent teaches multiple different reaction conditions, without guiding the skilled artisan to a particular set. D.I. 430 at 22-23. As such, the claims are indefinite.

II. REPLY ARGUMENTS TO EXCLUDE TESTIMONY

A. Dr. Spellman's Opinions Regarding Faham Should Be Excluded

Natera presents nothing to justify permitting Dr. Spellman to testify on Faham. Recognizing that Dr. Spellman's opinions are conclusory, Natera attempts to backfill by pointing to ¶¶ 131-34 of his report, which purportedly "identif[y] several limitations missing in Faham." D.I. 442 at 32. But these paragraphs are just background sections of Dr. Spellman's report that quote Faham with no analysis. D.I. 443-16 ¶¶ 131-134. Natera also points to paragraph 135 from the background, where Dr. Spellman states that the primer specific to the C region of TCR or BCR that is disclosed in Faham is not a universal primer. D.I. 442 at 32. But Dr. Spellman provides no support or explanation for this, nor does he explain the implications of this on validity. D.I. 443-16 ¶ 135.

Natera contends that ¶¶ 157-60 of Dr. Spellman's report "set forth his analysis" on validity.

D.I. 442 at 32-33. Dr. Spellman's so-called "analysis," however, is nothing more than naked assertions that Faham "does not teach" some limitations. D.I. 443-16 ¶ 159. Natera relies upon *EMC Corp. v. Pure Storage, Inc.*, 154 F. Supp. 3d 81, 94 (D. Del. Feb. 11, 2016). *See* D.I. 442 at 34. Yet, in that case, the expert ***explained*** how the accused product infringed under the doctrine of equivalents. *Id.* Dr. Spellman provides no explanation whatsoever.

Finally, Natera contends that Dr. Spellman explains "why a POSA would not be motivated or have a reasonable expectation of success by combining Faham with another prior art reference (Broude)." D.I. 442 at 32-33. But Dr. Spellman provided only a single sentence to support this sentence—that the "method of Broude is highly uneven, [and] a POSITA would have enormous concerns in scaling the multiplex PCR in Broude to large numbers of targets." D.I. 443-16 ¶ 160. Not only is this unsupported, but it is irrelevant because, as Dr. Spellman admits, the claims do not require even amplification. D.I. 434, Ex. B at 169:17-20.

B. Drs. Spellman's and Quackenbush's Signatera Opinions On Signatera Should Be Excluded

Natera presents no basis to justify permitting Drs. Spellman and Quackenbush to opine on whether Natera's Signatera product practices any Natera patents. Natera contends patentees are not required to provide a limitation-by-limitation analysis demonstrating that its products practice a patent. D.I 442 at 35. Not so. When, as here, a patentee asserts that commercial success supports nonobviousness, it must show nexus. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988). This requires showing "that the successful ***product is the invention disclosed and claimed in the patent***[.]" *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006). Natera must thus show that Signatera is "claimed," which requires a limitation-by-limitation analysis. *See id.*

Natera argues that Dr. Spellman cites a claim chart and "also provide[s] five paragraphs of

detail and additional citations to documents showing that Signatera practices" the '708 patent. D.I. 442 at 35. But none of the cited documents in either the chart or Dr. Spellman's report establishes that [redacted]. These documents do not mention the specific primers used in Signatera, and at most report on the annealing temperatures. *See* Exs. 16-20. Natera likely refuses to engage on the particulars for fear of further confirming indefiniteness. Regardless, Dr. Spellman has utterly failed to show that Signatera practices the key element of the '708 patent.

Finally, Natera does not dispute that Dr. Quackenbush did not map Signatera to the claims. D.I. 442 at 36. Instead, it incorrectly reiterates that no such claim mapping was required. *Id.* Even if Natera were correct that a full-fledged claim mapping is not required, it cannot be that an expert may be permitted to opine on embodying products simply by asserting in a single sentence that a product practices a bunch of patents, which is the very most Dr. Quackenbush has done.

C. Dr. Spellman's and Mr. Stoll's Opinions on Inventorship Should Be Excluded

Natera identifies no basis to permit Dr. Spellman and Mr. Stoll to testify on inventorship. Natera contends that "Dr. Spellman provided detailed rebuttal opinions on [Dr. Cooper's alleged] mischaracterization of the Asserted cfDNA Patents' disclosures and claimed inventions." *Id*. at 38. But the cited opinions from Dr. Spellman relate not to inventorship but to "whether the claimed inventions are enabled, adequately described and definite." D.I. 443-16 ¶ 223; *see also id.* ¶¶ 224-46. Dr. Spellman's actual "opinions" on inventorship do nothing but point out that the inventors submitted oaths to the Patent Office, which Dr. Spellman, a scientist at Oregon Health Sciences University, has no expertise in. As to Mr. Stoll, Natera does not deny that he has no expertise in the technology of the patents-at-issue. He has no basis to opine on whether any inventors engaged in technical work that could constitute an inventive contribution to the patents.

D. Dr. Wojcik's Opinions On Safe Harbor Are Baseless and Unreliable

Nothing in Natera's opposition refutes that Dr. Wojcik applied an erroneous interpretation of the Safe Harbor (provided by Natera's counsel) when forming his opinions. Rather, Natera cites deposition quotes from Dr. Wojcik where he was initially less concrete in his answers. *See* D.I. 442 at 42-43 (relying on Dr. Wojcik answering "not exactly"). While Dr. Wojcik cites the words of the statute, he applies an interpretation that is contrary to case law. For example, he argues that experimentation on devices for research and verification validation is not subject to the safe harbor if the product is not ***ultimately the subject of an FDA submission***. D.I. 434, Ex. V at 92:23-93:18. This is contrary to Supreme Court law. *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 202 (2005) ("There is simply no room in the statute for excluding certain information from the exemption on the basis of the phase of research in which it is developed.").

Further, Natera ***highlights*** Dr. Wojcik's testimony that uses of PCM for projects labeled "research use only" are somehow not able to take advantage of the Safe Harbor. D.I. 442 at 45. This is also contrary to *Merck. Merck,* 545 U.S. at 202. All research into new devices begins in a research use only phase. *See* D.I. 434, Ex. U ¶ 47 (Dr. Wojcik arguing that 90% of a product's development occurs in R&D). It would make little sense—and render the Safe Harbor ineffective—if researchers were only granted protection from infringement claims if they somehow avoided performing initial research into new devices.

E. Dr. Sullivan Failed To Properly Apportion

Natera's arguments that the BD-ArcherDX agreement represents a [redacted] royalty when ArcherDX only pays a [redacted] effective rate are baseless. Natera does not deny that Archer only pays an effective rate of [redacted] on its products to BD and that BD has never complained about the amount of royalties that they have received. Instead, Dr. Sullivan and Natera claim that there is no documentation that the royalty calculations by ArcherDX were in compliance with the agreement. But neither Dr. Sullivan, nor anyone else, analyzes the agreement to show this. As

such, Natera has not met its burden to show that the BD-ArcherDX agreement actually represents the rate they claim it does.

Natera's arguments that Dr. Sullivan properly accounted for the value of prior art molecular barcodes are similarly unavailing. Natera argues that "the proper exercise in assessing damages is not subtracting the value of all conventional elements from the value of the patented invention as a whole; rather, 'the question is how much new value is created by the novel combination, ***beyond the value conferred by the conventional elements alone***.'" D.I. 442 at 48. Natera ignores, however, that Dr. Sullivan's own analysis identifies the value of prior art conventional molecular barcodes—an improvement in the limits of detection by 95%. D.I. 434, Ex. AA at Attachment J-4. Dr. Sullivan then goes on to ***ignore*** that this improvement is attributable to prior art conventional elements and ***adds*** this value to the benefits provided by the accused technology. *Id.* This is the exact opposite of making a determination that would separate the value of a novel invention from preexisting conventional methods.

Natera's arguments regarding Dr. Sullivan's failure to properly address the benefits of personalization also fail. Natera claims that the decrease in the limits of detection are not attributable to personalization, yet the very chart that Dr. Sullivan relies upon (and reproduces in his report) clearly reaches a different conclusion. *See* D.I. 443-14 at 184 (showing the benefits of UMI separately in a ***fixed*** panel and in combination with personalization for a lower limit of detection). Dr. Sullivan cannot be permitted to rely on a chart exclaiming the benefits of personalization for the purpose of "adjusting" a royalty upwards by a factor of 8, yet then claim that personalization does not contribute to improved performance.

III. CONCLUSION

For the foregoing reasons, the Court should grant Defendants' motion.

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Respectfully submitted,

FARNAN LLP

/s/ Brian E. Farnan

Brian E. Farnan (#4089)
Michael J. Farnan (#5165)
919 North Market Street, 12th Floor
Wilmington, DE 19801
(302) 777-0300
bfarnan@farnanlaw.com
mfarnan@farnanlaw.com

Edward R. Reines (admitted *pro hac vice*)
Derek C. Walter (admitted *pro hac vice*)
Concord Cheung (admitted *pro hac vice*)
WEIL, GOTSHAL & MANGES LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065
Tel: (650) 802-3000
Fax: (650) 802-3100
edward.reines@weil.com
derek.walter @weil.com
concord.cheung@weil.com

Justin L. Constant (admitted *pro hac vice*)
WEIL, GOTSHAL & MANGES LLP
700 Louisiana, Suite 1700
Houston, TX 77002
Tel: (713) 546-5011
Fax: (713) 224-9511
justin.constant@weil.com

Attorneys for Invitae Corp., ArcherDX, Inc. and Archerdx, LLC